UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/469,733	12/21/1999	JEFFREY B. ETTER	42830-00060	5320

25231 7590 01/15/2003

MARSH, FISCHMANN & BREYFOGLE LLP
3151 SOUTH VAUGHN WAY
SUITE 411
AURORA, CO 80014

EXAMINER	
LIU, SAMUEL W	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 01/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/469,733	ETTER, JEFFREY B.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *21 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The drawings filed 21 October 2002 (Paper No. 18) have been approved by USPTO drafting. The response filed 21 October 2002 (Paper No. 16) amended claims 1-7, 10-11, 15-17, 19-20, 24, 27, 36-37, 39-41 and 45-47; and, presented a substitute specification that has been entered. Claims 1-48 are pending to which the following is or remains applicable. Please note that grounds of objection and/or rejection not explicitly restated and/or set forth below are withdrawn.

The specification on page 1 should be updated to reflect the status and relationship between 09/740573 and the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 10, 11-13, 40-41 and 46-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is indefinite as to lack of unit for "0.8" and "0.95". What reference is used to calculated these values? See also claims 11, 40 and 41. The dependent claims are also rejected.

Claims 46 and 47 recite "...have a degree of encapsulation ...greater than 50 percent". The recitation is unclear as to what type of "percent", *e.g.,* molarity percent, or weight percent or volume percent.

Claim 17 is unclear in regard to "if at all" because the terminology is an optional conditional phrase. See instead "the method of claim 1, wherein the cosolvent system has, from [certain percent] to less than 5% by weight, water.

Response to the rejection under 35 USC 112, the second paragraph

The comments in the response (page 6) filed 21 October 2002 have been considered but are unpersuasive as to the above issue in the stated ground of the rejection.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 7-13, 20-29, 42-44 and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by Manning, M. C. *et al.* (US Pat. No. 5770559, newly cited).

Manning *et al.* teach a method for making particles including a pharmaceutical material, *e.g.*, insulin, (see claim 30, column 5, lines 41-63 and Table 1 at column 18) wherein the particles are recovered in a powder form for direct pulmonary delivery (see claim 1 and examples 13 and 17), the method comprising the steps (*outlined in Figure 12*) of: (1) contacting the feed solution with the anti-solvent in order to precipitate the solid particles containing pharmaceutical polypeptide, *e.g.*, insulin (see claims 1 and 30) , and (2) separating the resultant particles (see column 11, lines 31-52, and column 12, lines 43-60). Manning *et al.* describe the

characteristics of the feed solution that contains: *a*) pharmaceutical substance (*e.g.*, insulin), *b*) organic solvent-I (*e.g.*, sodium dodecylsulphate) that dissolves the pharmaceutical substance, *c*) organic solvent-II (*e.g.*, dimethyl formamide), wherein *b*) and *c*) are mutually soluble (see column 11, lines 33-37) referring to a "co-solvent system". The Manning *et al.* teaching meets all limitation of claim 1. Thus, the patent anticipates claim 1 of the current application. Since insulin is much more soluble in sodium dodecylsulphate (organic solvent-I) than in hexane (organic solvent-II) (see Table I, at column 18, and column 6, lines 48-57), the Manning teaching is also applied to claim 2 of the current application.

Manning *et al.* teach the organic solvent is dimethyl formamide (see column 7, line 3-17), as applied claim 7 of the current application.

Manning *et al.* teach the organic solvent is ethanol (see Table I), as applied claims 8-9 of the current application.

Manning *et al.* teach anti-solvent precipitation where the fluid is at a reduced pressure of 0.8 to about 1.2 (see column 12, lines 3-13), as applied to claims 10-11 of the present application; and teach that the fluid includes carbon dioxide (see column 3, line 1-9, and column 12, lines 14-17), as applied to the application claims 12-13 and 42-44.

Manning *et al.* teach a biocompatible polymer co-dissolved with the pharmaceutical substance in the feed solution and incorporated into a powder (see column 3, lines 24-34, and abstract) that contains multiple components: pharmaceutical substance, *e.g.*, insulin (see column 5, lines 63 and claim 30), and biodegradable polymer (see column 14, lines 9-12), as applied to the application claims 20 and 22

Manning *et al.* teach the polymer, *e.g.*, a poly[ethylene glyco] (see column 14, lines 41-57, and example 14), sodium dodecylsulphate (organic solvent I) (see column 6, lines 33-47 and 52-53), and ethanol and acetone *etc.* (organic solvent II) (see Table 1). Because it is apparent that insulin peptide is more soluble in sodium dodecylsulphate than in the biopolymer and because the polymer is more soluble in organic solvent II, *e.g.*, acetone, the Manning *et al.* teaching is applied to the application claims 21 and 22.

Manning *et al.* teach that sodium dodecylsulphate [solvent I] is miscible with water and that the organic solvent *e.g.*, CCl_4 and acetone [solvent II] (see Table 1) are immiscible with water, as applied to the application claim 23.

Also, Manning *et al.* also teach methanol, ethanol and isopropanol (*i.e.*, C_1 –C_5 alkanol) as organic solvents (see column 7, lines 3-10), and as applied to the application claims 25-27; teach methylene chloride as the organic solvent (see Tables 2 and 4), as applied to the application claim 28; and teach a acid, *e.g.,* poly-glycolic acid dissolved in a volatile organic solvent (see example 14), as applied to the application claim 29.

Further, Manning *et al.* teach the poly-lactic acid in the feed solution (see example 14), as applied to claim 48 of the instant application.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) *A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

Claims 1-2, 7-13, 20-48 are rejected under 35 U.S.C. 103(a) as being obvious over Manning, M. C. *et al.* (US Pat. No. 5770559) taken with Debenedetti P. G. *et al.* (US Pat. No. 6063910) and Andersson M.-L. *et al.* (US Pat. No. 6372260).

Manning *et al.* teach a method for making particles including a pharmaceutical material, *e.g.*, insulin, (see claim 30, column 5, lines 41-63 and Table 1 at column 18) wherein the particles are recovered in a powder form for direct pulmonary delivery (see claim 1 and examples 13 and 17), the method comprising the steps (*outlined in Figure 12*) of: (1) contacting the feed solution with the anti-solvent in order to precipitate the solid particles containing pharmaceutical polypeptide, *e.g.*, insulin (see claims 1 and 30) , and (2) separating the resultant particles (see column 11, lines 31-52, and column 12, lines 43-60). Manning *et al.* describe the characteristics of the feed solution that contains: *a*) pharmaceutical substance (*e.g.*, insulin), *b*) organic solvent-I (*e.g.*, sodium dodecylsulphate) that dissolves the pharmaceutical substance, *c*) organic solvent-II (*e.g.*, dimethyl formamide), wherein *b*) and *c*) are mutually soluble (see column 11, lines 33-37) referring to a "co-solvent system". The Manning *et al.* teaching meets all limitation of claim 1. Thus, the reference patent anticipates claim 1 of the current application. Since insulin is much more soluble in sodium dodecylsulphate (organic solvent-I) than in hexane (organic solvent-II) (see Table I, at column 18, and column 6, lines 48-57), the Manning's teaching is also applied to claim 2 of the current application.

Manning *et al.* teach the organic solvent is dimethyl formamide (see column 7, line 3-17), as applied claim 7 of the current application.

Manning *et al.* teach the organic solvent is ethanol (see Table I), as applied claims 8-9 of the current application.

Manning *et al.* teach anti-solvent precipitation is conducted near critical relative to the anti-solvent fluid wherein the fluid is at a reduced pressure of 0.8 to about 1.2 (see column 12, lines 3-13), as applied to claims 10-11 of the present application; and teach that the fluid includes carbon dioxide (see column 3, line 1-9, and column 12, lines 14-17), as applied to the application claims 12-13 and 42-44.

Manning *et al.* teach a biocompatible polymer co-dissolved with the pharmaceutical substance in the feed solution and incorporated into a powder (see column 3, lines 24-34, and abstract) that contains multiple components: pharmaceutical substance, *e.g.*, insulin (see column 5, lines 63 and claim 30), and biodegradable polymer (see column 14, lines 9-12), as applied to the application claims 20 and 22

Manning *et al.* teach the polymer, *e.g.*, a poly[ethylene glyco] (see column 14, lines 41-57, and example 14), sodium dodecylsulphate (organic solvent I) (see column 6, lines 33-47 and 52-53), and ethanol and acetone *etc.* (organic solvent II) (see Table 1). Because it is apparent that insulin peptide is more soluble in sodium dodecylsulphate than in the biopolymer and because the polymer is more soluble in organic solvent II, *e.g.*, acetone, the Manning *et al.* teaching is applied to the application claims 21 and 22.

Manning *et al.* teach that sodium dodecylsulphate [solvent I] is miscible with water and that the organic solvent *e.g.*, CCl_4 and acetone [solvent II] (see Table 1) are immiscible with water, as applied to the application claim 23.

Manning *et al.* also teach methanol, ethanol and isopropanol (*i.e.*, C_1 –C_5 alkanol) as organic solvents (see column 7, lines 3-10), and as applied to the application claims 25-27; teach methylene chloride as the organic solvent (see Tables 2 and 4), as applied to the application claim 28; and teach a acid, *e.g.,* poly-glycolic acid dissolved in a volatile organic solvent (see example 14), as applied to the application claim 29.

Manning *et al.* teach the poly-lactic acid in the feed solution (see example 14), as applied to claim 48 of the instant application.

Also, Manning *et al.* teach a method comprising prior to forming solid particle that contains the pharmaceutical sustenance (*e.g.*, insulin), the substance forming a complex with a biopolymer molecule in a carrier solution (*i.e.*, *organic solvent*, see column 11, lines 35-37), as applied to claim 32.

While Manning *et al.* do not expressly teach the limitations as to means of introducing feed solution into the compressed anti-solvent fluid *etc.*

Debenedetti *et al.* teach preparing protein microparticles containing the bioactive polypeptide, *e.g.*, insulin (claim 8, column 6, lines 14-17, and Figures 6-7) *via* a method comprising formation of solid particles that contains the bioactive polypeptide using a compressed anti-solvent precipitation technique (see column 2, lines 23-60, and columns 4-8), as applied to claims 1 and 33-38 of the current application.

Also, Debenedetti *et al.* teach the organic solvents are non-aqueous, *e.g.*, ethanol, dimethylformamide (DMF), dimethylsulfoxide (DMSO) and acetic acid (see column 2, lines 30-44, and claims 1 and 4), as applied to the application claims 14, 17-18 and 30-31; and teach a mean of controlling contacting the protein solution with the compressed anti-solvent fluid and precipitation of the protein particle thereof (see column 4, lines 34-52, and column 5, lines 33-41), as applied to the application claims 15-16, 39-40 and 45-47.

Debenedetti *et al.* do not teach colloidal particle form of bioactive polypeptide in the feed solution. But, Andersson *et al.* teach a process for incorporating bioactive substance in pharmaceutical particles by forming an emulsion (a colloidal form) and precipitating the particles using compressed fluid anti-solvent precipitation technique (see abstract, and columns 2-5) wherein the emulsifier is a polymer (see patent claim 22), and teach that the emulsion is prepared by mixing a liquid, non-aqueous phase and a liquid, aqueous phases (see patent claims 1-27), as applied to the application claim 19. Also, Andersson *et al.* teach that organic solvents (*e.g.*, ethanol and ethylene chloride) act as modifier for emulsion of bioactive substance prior to contacting with the compressed anti-solvent fluid (see column 5, lines 28-34, and column 3, lines 51-54), as applied to claims 32-35 of the current application.

The above references do not explicitly mention of ratio of insulin to the organic solvent(s) and the ratio of insulin to the biopolymer; however, the optimal admixture of the solvents to achieve appropriate size of insulin particle would have been determined by one of ordinary skill in the art by routine optimization such that routine optimization would have resulted in weight ratio (from ≥ 5:95 to ~ 50:50, see claim 37) of the insulin to the polymer in the feed solution *etc.*, because Manning *et al.* teaches the weight ratio of the biodegradable polymer

to the pharmaceutical substance ranging from 10 to 1 to about 100 to 1 (see column 14, lines 22-26) depending on the application (teaches the ratio that would have included the ratio recited in claims 36-37). Thus, the skilled artisan would have manipulated the particle sizes *via* optimizing the parameters with regard to the ratio mentioned above, temperature and pressure applied to anti-solvent fluid *etc.*

One of ordinary skill in the art would have combined the teachings of the above references because the Manning *et al.* teach the method of preparing particles containing pharmaceutical polypeptide (including insulin) using the anti-solvent technique, the Debenedetti's patent teaches a mean of controlling contacting the protein solution with the compressed anti-solvent fluid and precipitation of the protein particle thereof, and the Andersson's patent teaches an alternative approach to prepare the particles via forming an emulsion of bioactive substance prior to anti-solvent-mediated precipitation of the particles containing the active substance.

In addition, when combined, the above references would have offered the following advantages: (1) controllable size of microparticles for drug delivery and microparticle/antisolvent technique disclosed thereof is particular useful for hydrophobic enzyme or protein of which insulin is a preferred protein (see column 2, lines 23-36), as taught by the Debenedetti *et al.* patent; (2) an improved and effective mean for incorporation of active protein into the particles for drug delivery since the incorporation step is critical for preparing anti-solvent-mediated precipitation of the particles from preparation system (see column 1, lines 35-40), which is by forming an emulsion of the active substance with biopolymer/polymer(see claims 1-27 and columns 2-5), as taught by the Andersson *et al.* patent, and (3) permitting pharmaceutical

substances that are substantially not soluble in an organic solvent to be solubilized via co-dissolving biodegradable polymer, which associates the substance, organic solvent along with amphiphilic material (see column 3, lines 24-34) prior to forming the particle containing pharmaceutical substance and separating the particle by the disclosed anti-solvent technique (see columns 11-12), as taught by Manning *et al.*

Based on the above motivation and the advantages, the expected result would have been the claimed method of manufacturing insulin particles. Because the Manning *et al.* teaching is directed to pulmonary delivery of the resultant particles and the Debenedetti *et al.* teaching is also directed to drug particles for therapeutic use, the skilled artisan would have a reasonable expectation of success that the methods claimed in the instant application would be successful. Thus, the claimed invention was *prima facie* obvious to make and use at the time it was made.

Claim Rejections - Provisional Rejection, Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130 (b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-18 of the instant application are provisionally rejected under the judicially created doctrine of double patenting over claims 1-4, 94, 95, 5, 6, 7, 8, 9, 10, 11, 13, 22, 14, 15 and 16 of copending Application No. 09740573. This is a provisional double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 2, 3, 4, 5, 6, 7, 10, 11, 22, 14, 15 and 16 of Application 09740573 are identical to claims 1, 2, 3, 4, 7, 8, 9, 12, 13, 15, 16, 17 and 18 of the instant application except that 09740573 set forth "a drug" while the current application claims set forth "insulin". Because claim 20 sets the limitation to the disclosed drug that "the drug is insulin", the claims of the current application and application 09740573 are obvious variations one another.

Claims 94 and 95 of Application 09740573 sets forth a concentration of the drug dissolved in the cosolvent system; in view of claim 20 that discloses that the said drug is insulin, claims 5 and 6 of the instant application are obvious variation of claims 94 and 95.

Claim 13 of Application 09740573 set forth the same disclosure as that of claim 14 of the instant application except the recitation "the drug" in Application 09740573. because the reason state in the precedence, the claim 13 of 09740573 and claim 14 of the current application are obvious variation each other.

Claims 8 and 9 of Application 09740573 set forth the common subject matter as that of claims 10 and 11 of current application but with different scope.

Therefore, the claims of the present application are not patentably distinct from the claims of Application No. 09740573.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483.

The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Samuel Wei Liu

January 7, 2003

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600